UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 04/02/2008

SUBJECT: PP#7E7227; Bifenthrin (128825). **Human-Health Risk Assessment** for a Section 3 Registration Request for Application of Bifenthrin and Establishment of Tolerances for Residues in/on Bushberries (Crop Subgroup 13B), Juneberry, Lingonberry, Salal, Aronia Berry, Lowbush Blueberry, Buffalo Currant, Chilean Guava, European Barberry, Highbush Cranberry, Honeysuckle, Jostaberry, Native Current, Sea Buckthorn, and Leaf Petioles (Crop Subgroup 4B).

Petition No.	7E7227	Decision No:	379758
DP No:	350900	40 CFR:	§180.442
Chemical No.:	128825	Class:	Synthetic Pyrethroid
Trade Names:	Capture 2EC, Capture LFR, Brigade 2EC, Brigade WSB	EPA Reg. Nos.:	279-3069; 279-3313; 279-3108, 279-3302
MRIDs:	47144501, 47144502, 47144503		

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The Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Stations of FL, MI, NJ, OR, TN, and TX, has submitted requests for Section 3 registrations for the application of bifenthrin to leaf petioles, subgroup 4B, [celery, cardoon, Chinese celery, celtuce, Florence fennel, rhubarb, and Swiss chard] and bushberries, subgroup 13B [blueberry (highbush and lowbush), currant, elderberry, gooseberry, and huckleberry]. In conjunction with this request, the petitioner has proposed the establishment of tolerances for bifenthrin [(2-methyl[1,1'-biphenyl]3-yl)methyl-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylate)] in/on:

Bushberry subgroup 13B	2.0 ppm
Juneberry	2.0 ppm
Lingonberry	2.0 ppm
Salal	2.0 ppm
Aronia berry	2.0 ppm
Blueberry, lowbush	2.0 ppm
Buffalo currant	2.0 ppm
Chilean guava	2.0 ppm
European barberry	2.0 ppm
Highbush cranberry	2.0 ppm
Honeysuckle	2.0 ppm
Jostaberry	2.0 ppm
Native currant	2.0 ppm
Sea buckthorn	2.0 ppm
Leaf petioles subgroup 4B	3.0 ppm

Concurrently, IR-4 requests the amendment of the following end-use products (EPs) containing bifenthrin as the active ingredient (ai) in order to include new uses on leaf petioles and bushberries: Capture® 2 EC Insecticide/Miticide (emulsifiable-concentrate formulation, EPA Reg. No. 279-3069), Brigade® 2EC (EPA Reg. No. 279-3313), Brigade® WSB (water-soluble bag, EPA Reg. No. 279-3108), and Capture® LFR Insecticide (flowable-concentrate formulation, EPA Reg. No. 279-3302). These EPs are proposed for multiple broadcast foliar applications at maximum seasonal rates of 0.5 pound (lb) ai/acre (A) using ground or aerial equipment. The proposed pre-harvest intervals (PHIs) are 1 day for bushberries and 7 days for leaf petioles.

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human-health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human-health that will result from the proposed and registered uses of bifenthrin.

A summary of the findings and an assessment of human-health risk resulting from the proposed and registered uses of bifenthrin are provided in this document. The hazard characterization was provided by PV Shah, Ph.D., (RAB1); the residue chemistry review, dietary exposure assessment, and aggregate exposure and risk assessment were provided by William Wassell (RAB1); the occupational/residential exposure assessment was provided by Mark Dow (RD); and the drinking water assessment was provided by Jose Melendez of the Environmental Fate and Effects Division (EFED).

Table of Contents

1.0 Executive Summary

References:

- Revised Preliminary HED Chapter for the Bifenthrin Tolerance Reassessment Eligibility Decision (TRED). DP Barcode: D283796. J. Liccione. 12/04/2002.
- Bifenthrin: Human-health Risk Assessment for Proposed Uses on Cilantro, Leafy Brassica Greens (subgroup 5b), Tuberous and Corm Vegetables (Subgroup 1c), Dried Shelled Peas and Beans (except Soybean) (Subgroup 6c) and Tobacco. DP Barcode: D310088. M. Rust-Clock, *et al.* 4/6/2006.
- Bifenthrin: PP#6E7125, PP#6E7126, PP#6E7127, PP#6E7128; Human-Health Risk Assessment for Proposed Uses on Mayhaw, Root Vegetables, (Except Sugar Beets, Crop Subgroup 1B), Peanut, Pistachio, Soybean, and Fruiting Vegetables (Crop Group 8). DP Number: 334154, W.D. Wassell *et al.,* 07/25/2007

Background

Bifenthrin is a neurotoxic insecticide acting through direct contact and ingestion, having a slight repellent effect. The primary biological effects of bifenthrin and other pyrethroids on insects and vertebrates are inhibition of the voltage-gated Ca^{2+} channels coupled with a stimulatory effect on the voltage-gated Na^{+} channels. All pyrethroids act as axonic poisons, affecting both the peripheral and central nervous systems, and share similar modes of action. Pyrethroids, including bifenthrin, stimulate repetitive action in the nervous system by binding to voltage-gated sodium channels, prolonging the sodium ion permeability during the excitatory phase of the action potential. This action leads to spontaneous depolarizations, augmented neurotransmitter secretion rate and neuromuscular block, which ultimately results in paralysis of the insect.

Bifenthrin is formulated as an EC, wettable-powder (WP), granular (G), or flowable-concentrate (FlC) product and has registered uses on a variety of commodities. Current tolerances (ranging from 0.05 to 10 ppm) are established in 40 CFR §180.442 for residues of bifenthrin in/on various plant and livestock commodities. Time-limited tolerances for orchard grass and sweet potato roots (0.05 ppm) have been established in conjunction with Section 18 emergency exemptions [40 CFR §180.442(2b)]. A tolerance of 0.05 ppm is established for residues of bifenthrin in food and feeds as a result of uses in food/feed handling establishments [40 CFR §180.442(2)]. Residential uses are registered for bifenthrin; however, no new residential uses are proposed in the subject actions.

A Tolerance Reassessment Eligibility Decision (TRED) was issued for bifenthrin in 2002 (reference above) and human-heath risk assessments were completed on 4/6/06 and 7/25/07. The TRED and risk assessments examined all registered and previously pending uses of bifenthrin. A complete discussion of the hazard assessment is included in these documents.

Dietary Exposure Assessment

Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

Acute Dietary Exposure and Risk

An acute population-adjusted dose (aPAD) is established based upon the acute neurotoxicity study in rats. In this study, the lowest-observed-adverse-effect-level (LOAEL) of 70.3 mg /kg/day is based on observations of mortality (females only), clinical and functional observation battery (FOB) findings and differences in motor activity. An uncertainty factor (UF) of 100x

(10x for inter-species extrapolations, 10x for intra-species variations, and a Food Quality Protection Act safety factor (FQPA SF) of 1x) was used to calculate the aPAD. The aPAD for bifenthrin is equal to 0.33 mg/kg/day.

A highly-refined, acute probabilistic dietary exposure and risk assessment was conducted for drinking water and all registered and pending uses of bifenthrin. Anticipated residue estimates (ARs) were developed based on the latest USDA's Pesticide Data Program (PDP) monitoring data 1998-2005, Food and Drug Administration (FDA) data, or field trial data for bifenthrin. ARs were further refined using the latest percent crop-treated data (%CT) and processing factors where appropriate.

EFED calculated Tier 1 estimated drinking water concentrations (EDWCs) for bifenthrin in ground and surface drinking water using the screening concentration in ground water (SCI-GROW) and FQPA Index Reservoir Screening Tool (FIRST) models, respectively. EDWCs in ground water were estimated as 0.003 ppb and 0.014 ppb in surface water. The acute drinking water concentration of bifenthrin in surface water (0.014 ppb) is based on the application of bifenthrin to lettuce at the highest application rate (0.5 lb ai/A/season) and the solubility of bifenthrin in water.

The acute dietary exposure estimates for food and drinking water are not of concern to HED (<100% of the aPAD) at the 99.9th percentile of exposure. Bifenthrin dietary exposure at the 99.9th percentile for food and drinking water for the U.S. population is 10% of the aPAD and 25% of the aPAD for all infants (<1 year old), the most highly-exposed population subgroup. These estimates include exposure from residues in drinking water.

Chronic Dietary Exposure and Risk

A chronic population-adjusted dose (cPAD) is established based upon the one-year oral toxicity study in dogs. In this study, the LOAEL of 2.7 mg /kg/day is based on observations of increased incidence of tremors in both sexes. An UF of 100x was used to calculate the cPAD. The cPAD for bifenthrin is equal to 0.013 mg/kg/day.

A refined chronic dietary exposure assessment was conducted for the registered and pending uses of bifenthrin using single point estimates of anticipated bifenthrin residues for food. The estimated surface water concentration of 0.014 ppb, based on application to lettuce at the highest application rate and the water solubility of bifenthrin, was also used for the chronic dietary assessment.

The chronic dietary exposure estimates for food and drinking water are not of concern to HED (<100% cPAD) for the U.S. population and all population subgroups. Bifenthrin dietary exposure for food and drinking water is 21% of the cPAD for the U.S. population and 55% of the cPAD for children 3-5 years old, the most highly-exposed population subgroup.

Cancer Dietary Risk

The Cancer Assessment Review Committee (CARC, 1992) recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human risk. The chronic exposure analysis exhibited exposures that were less than 100% RfD, and it is assumed that the chronic dietary endpoint is protective for cancer dietary exposure.

Residential Exposure and Risk
Bifenthrin has both indoor and outdoor residential uses. Adults may be exposed to bifenthrin residues during residential application of bifenthrin. Adults and children may be exposed to bifenthrin residues after application (post-application) of bifenthrin products in residential settings. Risk estimates were generated for residential handler exposures, and potential post-application contact with lawn, soil, and treated indoor surfaces using HED's Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessment, and dissipation data from a turf transferable residue (TTR) study. These estimates are considered conservative, but appropriate, since the study data were generated at maximum application rates.

Residential Handler Risk Estimates
Short- to intermediate-term dermal and inhalation exposures may occur for residential handlers of bifenthrin products. Residential handler risks from inhalation exposures to bifenthrin gas/vapor are considered unlikely, since the vapor pressure of bifenthrin is low. Inhalation exposure was assessed for aerosols/particulates during residential mixing, loading, and application of granular products. Short- and intermediate-term handler margins-of-exposure (MOEs) estimated for combined dermal and inhalation exposures were >100, and therefore, are not of concern to HED.

Residential Post-Application Risk Estimates
Adults and children may be potentially exposed to bifenthrin residues after application of bifenthrin products in residential settings. Short- and intermediate-term post-application dermal exposures for adults, and short- and intermediate-term post-application dermal and incidental oral exposures for children are anticipated. Risk estimates were generated for potential contact with lawn, soil, and treated indoor surfaces. Short- and intermediate-term risks estimated for post-application exposure for adults and children are not of concern to HED. Combined oral and dermal short-term exposures for children are not of concern to HED. Combined adult handler and post-application risk estimates (inhalation and dermal) associated with homeowner applied formulations are not of concern to HED.

Aggregate Risk
Because there is the potential for short- and intermediate-term, non-dietary post-application exposure of children and adults to bifenthrin when used as a residential treatment, aggregate risks were assessed. Short- and intermediate-term aggregate (dietary + residential) MOEs for the general U.S. population and any subpopulation of the general U.S. population are at least 180and this value is not of concern to HED (MOE ≤100). Chronic (>6 months) non-dietary post-application exposure to bifenthrin from a residential treatment is considered unlikely; therefore, chronic aggregate risk assessments were not performed.

Short- and Intermediate-term Endpoints
The short- and intermediate term dermal endpoints for use in risk assessment are established for bifenthrin. The effects seen were observations of clinical signs (staggered gait and exaggerated hindlimb reflex) and were identified from a 21 day dermal study in rats. The no-observable-adverse-effect-level (NOAEL) is 47.0 mg/kg/day. The level of concern (LOC) for occupational and residential dermal is a MOE of less than 100.

The short- and intermediate-term inhalation toxicological endpoints are established for bifenthrin. The inhalation endpoints are identified from a 90-day oral toxicity study in dogs. The

observations were increased incidence of tremors in both sexes. The NOAEL is 2.21 mg/kg/day. MOEs of less than 100 are considered risks of concern to HED.

Occupational Handler Risk
Based upon the proposed use pattern, HED expects the most highly-exposed occupational pesticide handlers (mixers, loaders, applicators) to be 1) mixer/loader using open-pour loading of liquids; 2) an aerial applicator, 3) an applicator using open-cab, ground-boom spray equipment. The proposed WP formulation consists of the product in water-soluble packages (WSP). A mixer/loader loading WSP was not assessed. HED considers WSP to be a "closed loading system" thereby reducing exposures to negligible amounts. Exposure from handling water-soluble packages is expected to be less than that experienced by mixer/loaders using open-pour techniques. HED believes most exposure durations will be short-term (1-30 days). However, the Science Policy Council for Exposure (ExpoSAC) maintains that it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1-6 months). Therefore, estimates for short- and intermediate-term risks are presented. **Provided that mixer/loaders wear protective gloves**, all MOEs are above 100, and, therefore, are not of concern to HED.

Occupational Post-Application Risk
Based on the proposed use pattern, HED has calculated post-application exposure and risk for workers exposed to bifenthrin residues following treatment. Workers engaging in activities such as hand harvesting, topping, stripping and irrigation activities were assessed. Standard assumptions were incorporated into the assessment to reflect conservative risk estimates. The MOE for the theoretically most highly-exposed post-application agricultural activity is 370, and is not of concern to HED. All other identified post-application activities are expected to have lower exposures and greater MOEs.

Based on the acute toxicity category classification for bifenthrin, the interim worker protection standard (WPS) restricted-entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures. The proposed end-use product labels list an REI of 12 hours.

HED Recommendations
The tolerances proposed by the registrant in the current petitions are listed below, along with HED's recommended tolerance levels.

Pending submission of a revised Section B (see requirements under 860.1200 Directions for Use) and a revised Section F (see requirements under 860.1550 Proposed Tolerances), the residue chemistry and toxicology databases support unconditional registration and establishment of permanent tolerances for the following:

Tolerance Summary for Bifenthrin.			
Crop Group or Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Bushberry subgroup 13B	2.0	1.8	*Bushberry subgroup 13-07B*
Juneberry	2.0	Not needed	Separate tolerances for new commodities listed in crop subgroup 13-07B are no longer required; refer
Lingonberry	2.0		
Salal	2.0		

Tolerance Summary for Bifenthrin.			
Crop Group or Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Aronia berry	2.0		to the Final Rule published in the Federal Register 12/7/07.
Blueberry, lowbush	2.0		
Buffalo currant	2.0		
Chilean guava	2.0		
European barberry	2.0		
Highbush cranberry	2.0		
Honeysuckle	2.0		
Jostaberry	2.0		
Native currant	2.0		
Sea buckthorn	2.0		
Leaf petioles subgroup 4B	3.0	3.0	

860.1200 Directions for Use

- There are now adequate residue data supporting bifenthrin use on head lettuce grown in CA. Therefore, the petitioner may submit a revised Section B to remove the existing restriction prohibiting use of bifenthrin on head lettuce grown in CA.

- Label revisions are required to remove the statement that emulsified oil may be substituted for water for aerial applications; the submitted crop field trials do not reflect the use of emulsified oil.

- HED notes that the draft label for 1.5 lb/gal FlC formulation states under Directions for Use that the product is for ground application only, and application by air is prohibited, but indicates under the specific use directions for leafy petiole vegetables and bushberries that the product may be applied by air. This discrepancy should be resolved.

860.1550 Proposed Tolerances

- The petitioner is required to submit a revised Section F to amend the proposed tolerance for Bushberry subgroup 13-07B and to reflect correct commodity definition as reflected in the tolerance summary table (above).

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

The petitioner has submitted draft labels for the 2 lb/gal EC formulations (Capture® 2EC Insecticide/Miticide; EPA Reg. No. 279-3069 and Brigade® 2EC Insecticide/Miticide; EPA Reg. No. 279-3313), the 10% WP formulation (Brigade® WSB Insecticide/Miticide; EPA Reg. No. 279-3108), and the 1.5 lb/gal FlC formulation (Capture® LFR; EPA Reg. No. 279-3302). Table 2.1 is a summary of the proposed application scenarios.

Table 2.1. Summary of Proposed Directions for Use of Bifenthrin.					
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Single Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)
Bushberries: blueberry, high and lowbush; currant, elderberry, gooseberry, and huckleberry					
Foliar, Broadcast, Ground (≥10 gal/A) or aerial (≥2 gal/A)	2 lb/gal EC [279-3069]	0.10	Not specified (NS)	0.5	1
	10% WP [279-3108]	0.10	NS	0.5	1
	2 lb/gal EC [279-3313]	0.10	NS	0.5	1
	1.5 lb/gal FlC [279-3302]	0.10	NS	0.5	1
	Use Directions and Limitations: For aerial applications, 1-2 quarts of emulsified oil may be substituted for 1-2 quarts of water in the finished spray. A minimum 7-day RTI is specified.				
Leafy Petiole Vegetables: celery, cardoon, Chinese celery, celtuce, Florence fennel, rhubarb, Swiss chard					
Foliar, Broadcast, Ground (≥10 gal/A) or aerial (≥2 gal/A)	2 lb/gal EC [279-3069]	0.10	NS	0.5	7
	10% WP [279-3108]	0.10	NS	0.5	7
	2 lb/gal EC [279-3313]	0.10	NS	0.5	7
	1.5 lb/gal FlC [279-3302]	0.10	NS	0.5	7
	Use Directions and Limitations: For aerial applications, 1-2 quarts of emulsified oil may be substituted for 1-2 quarts of water in the finished spray. A minimum 7-day RTI is specified.				
Lettuce, head					
Foliar, Broadcast, Ground (≥15 gal/A for 2 lb/gal EC and ≥20 gal/A for 10% WP) or aerial (≥5 gal/A)	2 lb/gal EC [279-3069]	0.10	NS	0.5	7
	10% WP [279-3108]	0.10	NS	0.5	7
	2 lb/gal EC [279-3313]	0.10	NS	0.5	7
	Use Directions and Limitations: For aerial applications of the EC formulation, 1-2 quarts of emulsified oil may be substituted for 1-2 quarts of water in the finished spray. A minimum 7-day RTI.				
At planting Soil banded, in-furrow, or broadcast soil surface Ground	1.5 lb/gal FlC [279-3302]	0.08	NS	0.1 (at plant) 0.5 (at plant + foliar applications of other bifenthrin products)	NS
	Use Directions and Limitations: Applications may be made as a 5-7 inch band over an open furrow (T-band), in-furrow with the seed, or broadcast over the entire acre on the soil surface.				

The following rotational crop restriction is specified for the 2 lb/gal EC, 10% WP, and 1.5 lb/gal FlC formulations: Crops for which bifenthrin tolerances exist may be rotated at any time. All other crops may be rotated 30 days following the final application of bifenthrin. The labels specify an REI of 12 hours for all formulations.

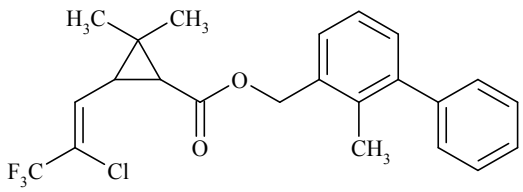
The draft labels for the 2 lb/gal EC formulations prohibit use in CA. In addition, these labels specify that the product may be applied through sprinkler including center pivot, lateral move, end tow, side (wheel) roll, traveler, big gun, solid set, or hand move irrigation systems. The draft labels for the 10% WP and 1.5 lb/gal FlC formulations specify that application through any type of irrigation system is prohibited.

HED notes that the draft label for 1.5 lb/gal FlC formulation states under Directions for Use that the product is for ground application only, and application by air is prohibited, but indicates under the specific use directions for leafy petiole vegetables and bushberries that the product may be applied by air. This discrepancy should be resolved by submission of a revised Section B.

Conclusions. The proposed use directions are adequate to allow evaluation of the residue data relative to the proposed use. However, since adequate field trial data are now available to support the use of the 2 lb/gal EC formulation on head lettuce grown in CA (Zone 10). The petitioner may submit a revised Section B to remove the existing restriction prohibiting use of bifenthrin on head lettuce grown in CA. Additionally, label revisions are required for the proposed EPs to remove the statement that emulsified oil may be substituted for water for aerial applications; the submitted crop field trials do not reflect the use of emulsified oil.

2.2 Structure and Nomenclature

Table 2.2. Nomenclature of Bifenthrin.

Compound	
Common name	Bifenthrin
Company experimental names	Capture® Insecticide/Miticide
IUPAC name	2-methylbiphenyl-3-ylmethyl (1*RS*,3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate or 2-methylbiphenyl-3-ylmethyl (1*RS*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate
CAS name	(2-methyl[1,1′-biphenyl]-3-yl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS #	82657-04-03
End-use products/EPs	2.0 lb ai/gal EC formulation (Capture 2EC; EPA Reg. No. 279-3069) 1.5 lb/gal FlC formulation (Capture® LFR; EPA Reg. No. 279-3313) 2.0 lb ai/gal EC (Brigade 2EC, EPA Reg. No. 279-3108) 1.5 lb/gal FlC formulation (Capture® LFR; EPA Reg. No. 279-3302)

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of the Technical Grade Bifenthrin.		
Parameter	**Value**	**Reference**
Melting range	68-70.6°C	Product Chemistry Chapter of the TRED
pH	NA[1]	
Density at 24°C	1.26 g/mL	
Water solubility	0.014 ppb	
Solvent solubility (g/100 mL)	8.9 in heptane and methanol 125 in acetone, chloroform, ether, methylene chloride, and toluene	
Vapor pressure (Pa) at 25°C	2.41×10^{-5}	
Dissociation constant (pK_a)	Not applicable	
Octanol/water partition coefficient (Kow)	$>1 \times 10^{6}$	
UV/visible absorption spectrum	NA	

[1] NA = information not available.

3.0 Hazard Characterization/Assessment

For a complete summary of the toxicology database, see the following documents:

- BIFENTHRIN - 3rd Report of the Hazard Identification Assessment Review Committee. TXR No. 0051570. B. Tarplee. 2/19/2003.
- *Revised Preliminary HED Chapter for the Bifenthrin Tolerance Reassessment Eligibility Decision (TRED)*. PC Code: 128825 DP Barcode: D283796. J. Liccione. 12/04/2002.
- Bifenthrin: PP#6E7125, PP#6E7126, PP#6E7127, PP#6E7128; Human-Health Risk Assessment for Proposed Uses on Mayhaw, Root Vegetables, (Except Sugar Beets, Crop Subgroup 1B), Peanut, Pistachio, Soybean, and Fruiting Vegetables (Crop Group 8), 7/25/07, W.D. Wassell, DP#: 371449.

3.1 Acute Toxicity Profile

Table 3.1. Acute Toxicity Profile – Bifenthrin.			
Guideline No./Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100/Acute oral toxicity	0013519	LD_{50} = 70.1 mg/kg (♂); 53.8 mg/kg (♀)	II
870.1200/Acute dermal toxicity	00132520	LD_{50} > 2,000 mg/kg	III
870.1300/Acute inhalation toxicity	46029703	Data waived. Acceptable atmosphere could not be generated with product.	IV
870.2400/Primary eye irritation	00132522	Non-irritant	IV
870.2500/Primary dermal irritation	00132521	Non-irritant	IV
870.2600/Dermal sensitization	00132523	Not a sensitizer	N/A

3.2 FQPA Considerations

3.2.1 Adequacy of the Toxicity Database

The Hazard Identification and Review Committee (HIARC) concluded that the toxicology database for bifenthrin is complete.

3.2.2 Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to bifenthrin. This is based on the observation of neurotoxicity (clinical signs) in the acute neurotoxicity, subchronic neurotoxicity, 2-generation reproduction, developmental toxicity, dermal toxicity, subchronic toxicity and chronic toxicity studies. In addition, FOB findings were observed in the acute and subchronic neurotoxicity studies. Since the last HIARC, the registrant submitted a DNT study, which establishes clear NOAEL for the adult and offspring toxicity. The NOAEL in adults and offspring is based on the clinical signs of neurotoxicity.

3.2.3 Determination of Susceptibility

Based on the results in developmental toxicity studies in rats and rabbits, there is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to bifenthrin. In the prenatal developmental (gavage) toxicity study in rats, a slight increase in the incidence of "hydroureter without hydronephrosis" was observed in fetuses at the highest dose tested (1.77 mg/kg/day); maternal toxicity (tremors) was also observed at this dose level, and the maternal and developmental NOAELs were equivalent at 0.88 mg/kg/day. This effect was not observed in the prenatal developmental (dietary) toxicity study in rats. In the prenatal developmental toxicity study in rabbits, there was no evidence of developmental toxicity at the highest dose tested.

Based on the results in a 2-generation reproduction study in rats, there was no quantitative or qualitative evidence of increased susceptibility of neonates (as compared to adults) to bifenthrin.

Based on the results of the developmental neurotoxicity (DNT) study in rats, there was no quantitative or qualitative evidence of increased susceptibility of neonates (as compared to adults) to bifenthrin. In this study, the maternal and offspring toxicity NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation) based on clinical signs of neurotoxicity. This study did not impact endpoints selected for various exposure scenarios.

3.2.4 Degree of Concern Analysis

There are no concerns or residual uncertainties for pre- and/or post-natal toxicity following exposure to bifenthrin.

3.2.5 Recommendation for a DNT Study

A DNT study with bifenthrin is available. This study does not show any evidence of increased susceptibility of offspring following exposure to bifenthrin. This study did not impact endpoints selected by the HIARC for various exposure scenarios.

3.2.6 FQPA SF for Infants and Children

The bifenthrin risk assessment team recommends that the 10X FQPA SF for increased susceptibility be reduced to 1X for all exposure scenarios. This recommendation is based on the following considerations:

- The toxicology database is complete.
- There are no residual uncertainties concerning pre- and post natal toxicity. There are no residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes field trial data and 100% CT for all proposed commodities. Anticipated residue values and %CT were used for some commodities. By using these assumptions, the acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. The FQPA SF recommended by the bifenthrin review team **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

Based upon the above-described data, the FQPA SF can be reduced to 1x since there are no residual uncertainties for pre and/or post-natal toxicity.

3.3 Hazard Identification and Toxicity Endpoint Selection

The strengths and weaknesses of the bifenthrin toxicology database were considered during the process of toxicity endpoint and dose selection. The selected toxicity endpoints are summarized in Table 3.3.

Table 3.3. Summary of Toxicological Doses and Endpoints for Bifenthrin.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and LOC for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary-general population, including infants and children	NOAEL = 32.8 mg/kg UF = 100 Acute RfD = 0.33 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF = 0.33 mg/kg/day	Acute neurotoxicity study in rats. LOAEL = 70.3 mg/kg/day based on observations of mortality (females only), clinical and FOB findings and differences in motor activity.
Chronic Dietary-general population, including infants and children	NOAEL = 1.3 mg/kg/day UF = 100 Chronic RfD = 0.013 mg/kg/day	FQPA SF = 1X cPAD = cRfD / FQPA SF = 0.013 mg/kg/day	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Short-Term (1-30 days) Incidental Oral	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Intermediate-Term (1-6 months) Incidental Oral	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Short-Term (1-30 days) Dermal	Dermal NOAEL = 47 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).
Intermediate-Term (1-6 months) Dermal	Dermal NOAEL = 47 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).
Long-Term (>6 months) Dermal	Dermal NOAEL = 47 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	21-day dermal study in rats. LOAEL = 93 mg/kg/day based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex).
Short-Term (1-30 days) Inhalation	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Intermediate-Term (1-6 months) Inhalation	NOAEL= 2.21 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	90-day oral toxicity study in dogs. LOAEL = 4.42 mg/kg/day based on observations of increased incidence of tremors in both sexes.

Table 3.3. Summary of Toxicological Doses and Endpoints for Bifenthrin.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and LOC for Risk Assessment**	**Study and Toxicological Effects**
Long-Term (>6 months) Inhalation	NOAEL= 1.3 mg/kg/day UF = 100 MOE= 100	Residential MOE = 100 FQPA SF = 1X Occupational MOE = 100	1-year oral toxicity in dogs. LOAEL = 2.7 mg/kg/day based on observations of increased incidence of tremors in both sexes.
Cancer (oral, dermal, inhalation)	**Classification: Category C** (possible human carcinogen). No Q_1* has been derived. The RfD approach recommended for cancer assessment.		

UF = uncertainty factor, FQPA SF = FQPA Safety Factor, NOAEL = no–observed-adverse-effect-level, LOAEL = lowest-observed-adverse-effect-level, RfD = reference dose (a = acute, c = chronic), PAD = population-adjusted dose, MOE = margin of exposure, LOC = level of concern, N/A = Not Applicable.

3.3.1 Levels of Concern for Margin of Exposure

The target MOEs for occupational and residential exposure risk assessments are as follows:

Table 3.3.1. Levels of Concern for Margin of Exposure			
Route	**Duration**		
	Short-Term (1-30 days)	**Intermediate-Term (1-6 Months)**	**Long-Term (>6 Months)**
Occupational (Worker) Exposure			
Dermal	100[a]	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

[a] Based on the conventional UF of 100X (10X for inter-species extrapolation and 10X for intra-species variation).

3.3.2 Recommendation for Aggregate Exposure Risk Assessments

The toxicity endpoints selected for these routes of exposure may be aggregated as follows: for short-, intermediate- and long-term aggregate exposure risk assessments, the oral, dermal and inhalation (oral equivalent) routes can be combined because of the common toxicity endpoints (clinical signs of neurotoxicity) via these routes.

3.4 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory

Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). Bifenthrin database did not indicate any endocrine mediated effects. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, bifenthrin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Dietary Exposure/Risk Characterization

4.1 Pesticide Metabolism and Environmental Degradation

References:

- Bifenthrin TRED, S. Levy, 21-AUG-2002; DP# 283808
- Bifenthrin: Human-health Risk Assessment for Proposed Uses on Cilantro, Leafy Brassica Greens (subgroup 5b), Tuberous and Corm Vegetables (Subgroup 1c), Dried Shelled Peas and Beans (except Soybean) (Subgroup 6c) and Tobacco. M. Rust-Clock, et. al. 4/6/2006
- 45794202.der
- PP#7E7227; Bifenthrin (128825). Section 3 Registration Request for Application of Bifenthrin to Bushberry (Crop Subgroup 13B), Juneberry, Lingonberry, Salal, Aronia Berry, Lowbush Blueberry, Buffalo Currant, Chilean Guava, European Barberry, Highbush Cranberry, Honeysuckle, Jostaberry, Native Current, Sea Buckthorn, and Leaf Petioles (Crop Subgroup 4B) and FMC Corporation's Field Trial Data on Head Lettuce. Summary of Analytical Chemistry and Residue Data. Pending, W.D. Wassell, DP#: 342661
- Memo, M. Flood, 07/23/93, PP#7F3456

4.1.1 Metabolism in Primary Crops and Livestock

4.1.1.1 Metabolism in Primary Crops

The nature of bifenthrin residues in plants is adequately understood based on the available metabolism studies with corn, cotton, and apple. HED previously determined that for purposes of tolerance expression and risk assessment, the residue of concern in cotton and apple commodities is bifenthrin *per se* (Memoranda, M. Flood, 12/24/87 and N. Dodd, 7/02/87). After re-examining the cotton and apple metabolism data and additional corn metabolism data, the HED Metabolism Committee (Memo, M. Flood, 7/23/93) reaffirmed that the residue of concern in plant commodities is bifenthrin *per se*.

In conjunction with a previous risk assessment for use on tuberous and corm vegetables, IR-4 submitted a metabolism study on potatoes reflecting both soil and foliar applications of [^{14}C] bifenthrin. The potato study is adequate and the results from the metabolism study support HED's previous determination that the residue of concern is bifenthrin *per se.* The bifenthrin review team agrees with these decisions.

4.1.1.2 Metabolism in Livestock

Adequate studies are available depicting the metabolism of [^{14}C]bifenthrin in ruminants and poultry. The nature of the residue in livestock is adequately understood based on goat and hen metabolism studies. The HED Metabolism Committee determined that for purposes of tolerance expression and risk assessment, the residue of concern in livestock is bifenthrin *per se* (Memo, M. Flood, 7/23/93). The bifenthrin review team agrees with this decision.

4.1.2 Metabolism in Rotational Crops

Adequate confined and field rotational crop studies are available. Based on the confined study, HED has concluded that the residue of concern in rotational crops is the parent compound only. The bifenthrin review team agrees with this decision.

4.1.3 Analytical Methodology

Adequate gas chromatography/electron-capture detection (GC/ECD) methods are available for enforcing tolerances for bifenthrin residues in plant and livestock commodities. The available methods for plant commodities generally involve extraction of the sample with acetone, partitioning with hexane, purification using a Florisil column, and analysis of residues by GC/ECD. The limit of quantitation (LOQ) for these methods is 0.05 ppm.

Residues of bifenthrin in/on blueberry and celery were determined using a GC/ECD method (FMC Report P-2132M). For this method, residues are extracted with hexane using the Dionex ASE-200, concentrated, and cleaned up using a Florisil column, then analyzed by GC/ECD. The validated LOQ for bifenthrin is 0.05 ppm, and the reported limit of detection (LOD) is 0.01 ppm. The method was adequately validated in conjunction with analysis of samples from the field trials.

4.1.4 Environmental Degradation

References:

- Tier I Estimated Environmental Concentrations of Bifenthrin for the Use in the Human-Health Risk Assessment. 03/05/2008, J. Melendez
- Memo, 6/21/2002, S. Knizer, TXR# 0050887

The environmental fate database for bifenthrin is complete enough to characterize drinking water exposure. The submitted data indicate that bifenthrin is relatively persistent under both laboratory and field conditions. Bifenthrin is relatively immobile in four soils tested. Due to its low mobility, bifenthrin is not likely to reach subsurface soil environments (lower microbial activity) or ground waters. Various terrestrial field dissipation studies confirm that bifenthrin remains mostly in the upper soil level. Due to its low solubility and high level of binding it appears that bifenthrin would remain bound to the soils during run-off events and it may reach surface waters if the run-off event is accompanied by erosion.

The HED MARC concluded that the parent compound, bifenthrin *per se*, should be the residue of concern for risk assessment in drinking water based on its persistence and the absence of major

degradates in laboratory studies (Memo, 6/21/2002, S. Knizer, TXR# 0050887). The bifenthrin review team agrees with this decision.

4.1.5 Food Residue Profile

The field trials with bifenthrin on celery and blueberries are adequate. An adequate number of trials were conducted reflecting the proposed use patterns in the appropriate geographic regions, and the appropriate commodities were collected at the proposed PHIs. Samples were analyzed using adequate analytical methods. Tolerance levels for residues in/on bushberry (subgroup 13-07B) and leaf petioles (subgroup 4B) were determined using the North American Free Trade Agreement (NAFTA) maximum residue limits (MRL)/Tolerance Harmonization Spreadsheet.

Blueberries: IR-4 has submitted field trial data for the use of bifenthrin on blueberries. At each trial site, five foliar directed/broadcast applications of the 2 lb/gal EC formulation were made at 4- to 8-day RTIs to blueberries at 0.093-0.106 lb ai/A/application, for a total seasonal rate of 0.498-0.507 lb ai/A. At four trials, a second treated plot received five foliar direct/broadcast applications of 10% WP at 0.096-0.102 lb ai/A/application, with 6- to 8-day RTIs, for a total seasonal rate of 0.492-0.499 lb ai/A. At each trial, samples were harvested at commercial maturity, 1 day after the last application of bifenthrin. In the submitted field trials, maximum residues of bifenthrin were 1.61 ppm and 1.06 ppm, respectively, for trials with the EC and WP formulations. The results of the blueberry trials are summarized in Table 4.1.5a.

Table 4.1.5a. Summary of Residue Data from Blueberry Field Trials with Bifenthrin.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	EP	Residue Levels (ppm)					
				n	Min.	Max.	HAFT[1]	Mean	Std. Dev.
Proposed Use Pattern: Maximum Seasonal Rate of 0.5 lb ai/A with a 1-day PHI.									
Blueberry	0.498-0.509	1	2 lb/gal EC	18	0.36	1.61	1.36	0.80	0.34
	0.492-0.499	1	10% WP	8	0.37	1.06	0.91	0.65	0.28

[1] HAFT = Highest-Average Field Trial result.

Celery: IR-4 has submitted field trial data for the use of bifenthrin on celery in response to a data gap specified in DP# 277993 (8/15/02, S. Levy). At each treated plot, five foliar directed/broadcast applications of either the 2 lb/gal EC or 10%WP formulation of bifenthrin were made at 6- to 8-day RTIs to celery at 0.096-0.106 lb ai/A/application, for a total seasonal rate of 0.497-0.515 lb ai/A. Celery samples were harvested at commercial maturity, 6- to 8-days after the last application of bifenthrin. In these trials, residues of bifenthrin were 0.11-1.78 ppm and 0.06-1.16 ppm in/on celery, respectively, for trials with the EC and WP formulations.

Table 4.1.5b. Summary of Residue Data from Celery Trials with Bifenthrin.

Commodity	EP	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm)					
				N	Min.	Max.	HAFT[1]	Mean	Std. Dev.
Proposed Use Pattern: Maximum Seasonal Rate of 0.5 lb ai/A with a 7-day PHI.									
Celery	2 lb/gal EC	0.497-0.514	6-7	8	0.11	1.78	1.49	0.75	0.54
Celery	10% WP	0.499-0.515	6-7	8	0.06	1.16	1.07	0.56	0.38

[1] HAFT = Highest-Average Field Trial result.

4.1.5.1 Tolerance Summary

The bifenthrin tolerances proposed by the registrants in the subject petition are listed below in Table 4.1.5.1, along with HED's recommended tolerance levels. Tolerance levels for residues of bifenthrin in/on bushberries (subgroup 13-07B) and leaf petioles (subgroup 4B) were determined using the NAFTA MRL/Tolerance Harmonization Spreadsheet.

Table 4.1.5.1. Tolerance Summary for Bifenthrin in/on Bushberries and Leaf Petioles.

Crop Group or Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Bushberry subgroup 13B	2.0	1.8	*Bushberry subgroup 13-07B*
Juneberry	2.0	Not needed	Separate tolerances for new commodities listed in crop subgroup 13-07B are no longer required; refer to the Final Rule published in the Federal Register 12/7/07.
Lingonberry	2.0		
Salal	2.0		
Aronia berry	2.0		
Blueberry, lowbush	2.0		
Buffalo currant	2.0		
Chilean guava	2.0		
European barberry	2.0		
Highbush cranberry	2.0		
Honeysuckle	2.0		
Jostaberry	2.0		
Native currant	2.0		
Sea buckthorn	2.0		
Leaf petioles subgroup 4B	3.0	3.0	

4.1.6 International Residue Limits

There are currently no established Codex, Canadian, or Mexican MRLs for bifenthrin in/on the proposed commodities. Therefore, harmonization is not an issue for the subject petition.

4.1.7 Drinking Water Residue Profile

Drinking Water Estimates
The EDWCs for bifenthrin were calculated based on a maximum application rate of 0.5 lb ai/A/season to lettuce. The acute drinking water concentration in surface water is 0.0140 ppb of bifenthrin, based on aerial applications to lettuce. The cancer/chronic drinking water concentration is 0.0140 ppb (based on applications of lettuce, highest application rate). The SCI-GROW generated EDWC is 0.003 ppb of bifenthrin, which is recommended for use in both acute and chronic exposures. Because of the very low solubility of bifenthrin, the EDWCs did not exceed 0.0140 ppb (the solubility of bifenthrin in water).

Table 4.1.7. Tier 1 Estimated Drinking Water Concentrations for Bifenthrin.			
Drinking Water Source (Model Used)	Use (Rate Modeled)	Maximum EDWC (ppb)	
Groundwater (SCI-GROW)	Lettuce (0.5 lb. ai/A/season)	Acute and Chronic	0.0030
Surface water (FIRST)	Lettuce (0.5 lb. ai/A/season)	Acute	0.0140
	Lettuce (0.5 lb. ai/A/season)	Chronic	0.0140

4.2 Dietary Exposure and Risk

Acute and chronic dietary exposure and risk assessments were conducted using DEEM-FCID™, Version 2.03, which uses food consumption data from the USDA's CSFII from 1994-1996 and 1998. The analyses were performed as part of a registration action; (1) to support a Section 3 Registration for use on bushberries (subgroup 13-07B) and leaf petioles (subgroup 4B); and (2) to include drinking water estimates reflecting the new uses.

EFED calculated the ground and surface drinking water Tier 1 EDWCs for bifenthrin new uses using SCI-GROW and FIRST models. It was found that lettuce is still the use with the major exposure and the highest PCA, and, therefore, the drinking water assessment results did not change from the previous ones. The EDWCs for bifenthrin were calculated based on a maximum application rate of 0.5 lb ai/A/season and the EDWCs in ground water were estimated as 0.003 ppb and 0.014 ppb in surface water.

4.2.1 Acute Dietary Exposure and Risk

A highly-refined, acute probabilistic dietary exposure and risk assessment was conducted for all supported (and pending) food uses and drinking water. ARs were developed based on the latest USDA PDP monitoring data 1998-2005, FDA data, or field trial data for bifenthrin. ARs were further refined using the latest %CT data and processing factors where appropriate. The EDWC of 0.014 ppb, based on application to lettuce at the highest application rate, was used to account for exposure from residues in water.

The acute dietary exposure estimates for food and drinking water are below HED's level of concern (<100% aPAD) at the 99.9th percentile of exposure. Bifenthrin dietary exposure at the 99.9th percentile for food and drinking water is 10% of the aPAD for the U.S. population and 25% of the aPAD for all infants (<1 year old), the most highly-exposed population subgroup.

Table 4.2.1. Results of Bifenthrin Acute Dietary (Food + Drinking Water) Exposure Analysis Using DEEM FCID.			
Population Subgroup	**aPAD (mg/kg/day)**	**99.9th Percentile**	
		Exposure (mg/kg/day)	**% aPAD**
General U.S. Population	0.33	0.034	10
All Infants (< 1 year old)	**0.33**	**0.084**	**25**
Children 1-2 years old	0.33	0.059	18
Children 3-5 years old	0.33	0.052	16
Children 6-12 years old	0.33	0.044	13
Youth 13-19 years old	0.33	0.026	8.0
Adults 20-49 years old	0.33	0.018	5.5
Adults 50+ years old	0.33	0.014	4.4
Females 13-49 years old	0.33	0.018	5.4

4.2.2 Chronic Dietary Exposure and Risk

A refined chronic dietary exposure assessment was also conducted for drinking water and the supported food uses of bifenthrin using single point estimates of anticipated bifenthrin residues, including %CT for food/feed crops. The EDWC of 0.014 ppb, based on application to lettuce at the highest application rate, was used for the chronic dietary assessment.

The chronic dietary exposure estimates for food and drinking water are below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Bifenthrin dietary exposure for food and drinking water is 21% of the cPAD for the U.S. population and 55% of the cPAD for children 3 to 5 years old, the most highly-exposed population subgroup.

Table 4.2.2. Results of Chronic Dietary (Food + Drinking Water) Exposure and Risk for Bifenthrin.		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD**
General U.S. Population	0.0028	21
All Infants (< 1 year old)	0.0030	23
Children 1-2 years old	0.0067	52
Children 3-5 years old	**0.0072**	**55**
Children 6-12 years old	0.0053	41
Youth 13-19 years old	0.0027	21
Adults 20-49 years old	0.0020	16
Adults 50+ years old	0.0018	14
Females 13-49 years old	0.0021	16

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

- *Bifenthrin: REVISED Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Eligibility Decision (TRED) Document.* S. Weiss. D286358. 10/25/2002.

Bifenthrin products are available to homeowners for indoor and outdoor application to residential premises. Adults and children may be potentially exposed to bifenthrin residues resulting from application.

Potential exposure and risk to residents (or "homeowners") have been assessed previously by HED. Information for this section was adapted from previous residential assessment for bifenthrin performed in 2002 (see reference above). Since completion of the last residential assessment, no product cancellations or new uses have occurred that would alter the conclusions. A summary of the exposure and risk resulting from residential uses of bifenthrin is provided below. These exposure estimates were used in the aggregate risk assessment which appears in Section 7.0 of this document.

5.1 Residential Handler Exposure

End-use products containing bifenthrin are formulated as ready-to-use-sprays, emulsified concentrates, wettable powders, granulars, pelletized tablets, and pressurized liquids.

The current maximum application rates of granulars and liquids by lawn-care operators (LCOs) are 0.4 and 0.3 lb ai/acre, respectively. For liquid and granular formulations applied by homeowners, the maximum rate is 0.2 lb ai/acre. In a letter to the Agency dated September 16,

2002, FMC agreed to lower the maximum rate for all turf uses to 0.2 lb ai/acre. Bifenthrin products may be applied by pest-control operators (PCOs) and homeowners in and around homes as a spray in concentrations of up to 0.06%. The majority of residential labels do not specify frequency of application.

Short- and intermediate-term exposures may occur for residents applying bifenthrin products. Chronic exposures are not anticipated for residential handlers. The exposure and risk for residential handlers were assessed using the revised draft SOPs for Residential Exposure Assessment, and includes surrogate data from the Pesticide Handlers Exposure Database (PHED) Outdoor Residential Exposure Task Force (ORETF). Since PHED and ORETF do not include data for ready-to-use spray bottle application, data from a proprietary study were used to estimate exposure (MRID 44739301).

The major exposure scenarios for non-occupational (residential) handler exposures are as follows:

* Mixing/loading/applying liquids for low-pressure handwand application.
* Mixing/loading/applying liquids for hose-end sprayer application.
* Mixing/loading/applying liquids for backpack sprayer application.
* Paintbrush application.
* Loading/applying a granular for belly-grinder application.
* Loading/applying a granular for push-type spreader application.
* Applying a granular with bare hands.
* RTU spray bottle application.

The most likely residential handler exposure scenario resulting in the highest exposure and risk is for loading/applying granular formulation by belly-grinder application. The short- and intermediate-term MOEs are 300 for dermal and 25,000 for inhalation, resulting in a combined MOE of 300. The exposure for this use is not of concern to HED.

5.2 Residential Post-application Exposure

Adults and children may be potentially exposed to bifenthrin residues after application of bifenthrin products in residential settings. Short- and intermediate-term post-application dermal exposures for adults, and short- and intermediate-term post-application dermal and incidental oral exposures for children are anticipated. Long-term exposure is not expected. Risk estimates were generated for potential contact with lawn, soil, and treated indoor surfaces using HED's Draft SOPs for Residential Exposure Assessment, and for the lawn scenarios, dissipation data from a chemical-specific TTR study. Indoor surface residues in homes were based on crack and crevice data collected for bifenthrin and malathion. These estimates are considered conservative screening level estimates, since the study data were adjusted to reflect maximum application rates. The scenarios that result in the highest exposure are summarized in Table 5.2.

Table 5.2. Summary of Residential Post-Application Risk for Bifenthrin.				
Exposure Scenario	Population	Route of Exposure	Short-Term MOE	Intermediate-Term MOE
Indoor: High-Contact Activity	Adults	Dermal	3100	3100
	Toddlers	Dermal Oral	1800 2600	1800 5500
Outdoor: High-Contact Activity on Turfgrass	Adults	Dermal	2300	4500
	Toddler	Oral and Dermal	740 Oral 1400 Dermal	1600 Oral 2700 Dermal

5.3 Other (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for bifenthrin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from dietary and residential sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Short-term aggregate risk assessment is required for bifenthrin due to the potential for residential exposure. The common toxicological effect observed across the oral and dermal routes of exposure is clinical signs of neurotoxicity. An aggregate MOE was calculated by taking the inverse of the sum of inverse MOEs for dietary and non-dietary (incidental oral and dermal) exposure pathways.

6.1 Acute Aggregate Risk

No acute residential/recreational exposures are expected. Since the dietary assessment included food and water, the exposures in Table 5.2.1 represent acute aggregate exposures. The acute

aggregate risk estimates are not of concern to HED.

6.2 Short- and Intermediate-Term Aggregate Risk

Because there is the potential for short- and intermediate-term, non-dietary exposure of children and adults to bifenthrin as a residential treatment (indoors and outdoors), it is appropriate to aggregate these exposures with dietary (food and water) exposure. Adults can be exposed through the residential application of bifenthrin via dermal and inhalation routes and through post-application exposure via the dermal route (treated turf). Children might be exposed following application in residential settings via dermal and incidental oral routes. HED believes that if a toddler were to be exposed to bifenthrin granules, it would most likely be episodic; that is, a one-time occurrence, and not likely to be repeated. Therefore, this episodic scenario was not aggregated with dietary exposure.

Residential exposure and risk have been summarized based on HED residential risk assessments for the existing uses of bifenthrin. Those scenarios resulting in the highest exposure and risk for adults and children have been summarized in Table 6.2.1. These exposures were used to calculated short- and intermediate-term aggregate risk by combining residential exposure with that from dietary sources.

Table 6.2.1. Summary of Residential Risk Resulting in Highest Exposure and Risk for Bifenthrin.

Population	Exposure Scenario		Route of Exposure	Short-Term MOE
Adults	Loading/applying granulars with a belly-grinder	Handler	Dermal and Inhalation	300 Dermal 25,000 Inhalation
	Hose-end Sprayer Application	Handler	Dermal and Inhalation	97,000 Inhalation 3000 Dermal
		Post-Application	Dermal	2300
	Liquid Structural Wood Treatment with Paintbrush	Handler	Dermal and Inhalation	23,000 Inhalation 600 Dermal
		Post-Application	No exposure expected due to low accessibility to treated areas (termite control).	
	Indoor: Liquid Crack and Crevice Spray	Handler	Dermal and Inhalation	210,000 Inhalation 14,000 Dermal
		Post-Application	Dermal	3100
Toddler	Outdoor: High Contact Activity on Turfgrass	Post-Application	Hand-to-Mouth/Oral	740
			Mouthing Treated Turf	3000
			Soil Ingestion	220,000
			Dermal	1400

[1] Combined MOE for handlers since dermal and inhalation endpoints (clinical signs) [1/(1/MOE-dermal)+(1/MOE-inhalation)].

The short- and intermediate-term NOAEL for non-dietary **oral** exposure is based on the 90-day oral toxicity study in dogs (NOAEL = 2.21 mg/kg/day). The short- and intermediate-term NOAEL for **dermal** exposure is based on the 21-day dermal toxicity study in the rat (NOAEL = 47 mg/kg/day). The common toxicological effect observed across the oral and dermal routes of exposure is clinical signs of neurotoxicity. The aggregate LOC (MOE) is 100.

The results of the short- and intermediate-term aggregate risk assessment for various subpopulations based on age are reported in Table 6.2.2. Short- and intermediate-term aggregate (dietary + residential) MOEs for the general U.S. population and any subpopulation of the general U.S. population are greater than or equal to 180 and therefore are not of concern to HED.

Table 6.2.2. Short- and Intermediate-Term Aggregate Risk for Bifenthrin.

Population	Dietary MOE[1]	Non-dietary Oral MOE[2]	Dermal MOE[3]	Inhalation MOE[4]	Aggregate MOE[5]
General U.S. Population	790	N/A	300	25,000	220
All Infants (<1 yr old)	740	590	1400	N/A[6]	270
Children 1-2 yrs. Old	330	590	1400		180
Children 3-5 yrs. Old	310	590	1400		180
Children 6-12 yrs. Old	420	N/A	1400		320
Youth 13-19 yrs. Old	820		1400		520
Adults 20-49 yrs. Old	1100		300	25,000	230
Adults 50+ yrs. Old	1200		300	25,000	240
Females 13-49 yrs. Old	1100		260	25,000	210

[1] Dietary MOE = [(short- or intermediate-term oral NOAEL)÷(chronic dietary exposure)]; NOAEL = 2.21 mg/kg/day; chronic dietary (food + water) exposures (see Table 5.2.2) were utilized as surrogates for short- and intermediate-term exposures.
[2] Non-dietary oral MOE = [(short- or intermediate-term oral NOAEL)÷(sum of all high-end incidental oral residential exposure)]; NOAEL=2.21 mg/kg/day; chronic dietary (food + water) exposures (see Table 4.2.2) were utilized as surrogates for short- and intermediate-term exposures.
[3] Dermal MOE = [(short- or intermediate-term dermal NOAEL)÷(high-end dermal residential exposure)]; NOAEL=47 mg/kg/day; structural wood treatment (paintbrush application) used for adult estimates.
[4] Inhalation MOE = [(short- or intermediate-term inhalation NOAEL)÷(high-end dermal residential exposure)]; NOAEL=2.21 mg/kg/day.
[5] Aggregate MOE (dietary and residential) = 1÷[(1÷dietary MOE) + (1÷non-dietary oral MOE) + (1÷dermal MOE) + (1÷inhalation MOE)]; values expressed to 2 significant figures; Inhalation MOE based on adult residential handler exposure.
[6] N/A = not applicable.

6.3 Long-Term (Chronic) Aggregate Risk

A chronic (non-cancer) aggregate risk assessment was not performed, because chronic residential exposure to bifenthrin (*i.e.*, >6 months) is not considered likely to occur based upon the use patterns.

6.4 Cancer Risk

The CARC (1992) recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human risk. The chronic exposure analysis revealed <100% RfD, and it is assumed that the chronic dietary endpoint is protective for cancer dietary exposure.

7.0 Cumulative Risk Characterization/Assessment

Bifenthrin is a member of the pyrethroid class of pesticides. EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, available data show that there are multiple types of sodium channels and it is currently unknown whether the pyrethroids as a class have similar effects on all channels or whether modifications of different types of sodium channels would have a cumulative effect. Nor do we have a clear understanding of effects on key downstream neuronal function, e.g., nerve excitability, or how these key events interact to produce their compound specific patterns of neurotoxicity. Without such understanding, there is no basis to make a common mechanism of toxicity finding. There is ongoing research by the EPA's Office of Research and Development and pyrethroid registrants to evaluate the differential biochemical and physiological actions of pyrethroids in mammals. When available, the Agency will consider this research and make a determination of common mechanism as a basis for assessing cumulative risk. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure/Risk Pathway

8.1 Short-/Intermediate-Term Handler Risk

Based upon the proposed use pattern, HED expects the most highly-exposed occupational pesticide handlers (mixers, loaders, applicators) to be: 1) mixer/loader using open-pour loading of liquids; 2) an aerial applicator, 3) an applicator using open-cab, ground-boom spray equipment. A mixer/loader loading water-soluble packages is NOT assessed. HED considers water-soluble packaging to be a "closed loading system" thereby reducing exposures to negligible amounts. Exposure from handling water-soluble packages is expected to be less than that experienced by mixer/loaders using open-pour techniques. HED believes most exposure durations will be short-term (1-30 days). However, the ExpoSAC maintains that it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1-6 months). Therefore, estimates for short- and intermediate-term risks are presented.

It is expected that some private applicators may perform all tasks; that is, mix, load and apply the material. However, HED ExpoSAC draft SOP (dated: 3/29/00) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as

handwands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand-held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, air-blast sprayers, or high-pressure handwand sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical-resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were available with which to assess potential exposure to occupational pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline"; that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary.

The RAB1 toxicology team also identified short- and intermediate-term inhalation toxicological endpoints. The inhalation endpoints are identified from a 90-day oral toxicity study in dogs. The observations were increased incidence of tremors in both sexes. The NOAEL is 2.21 mg/kg bw/day. MOEs less than 100 are of concern to HED.

The CARC (1992) has characterized bifenthrin as Category C (possible human carcinogen) and recommended that for the purpose of risk characterization, the RfD approach should be used for quantification of human cancer risk. Since no cancer potency factor was identified, a cancer risk assessment is not necessary.

See Table 8.1 for a summary of estimated exposures and risks to occupational pesticide handlers. In this case, the toxicological effects are similar (*i.e.*, clinical signs of neurological) for the dermal and inhalation routes although they were identified from different studies. Therefore, separate dermal and inhalation MOEs were calculated which were then used to calculate combined MOEs.

Table 8.1. Summary of Exposure & Risk for Occupational Handlers Applying Bifenthrin.					
Unit Exposure[1] Mg ai/lb handled	**Applic. Rate[2]** lb ai/unit	**Units Treated[3]**	**Avg. Daily Exposure[4]** mg ai/kg bw/day	**MOE[5]**	**Combined MOE[6]**
Mixer/Loader Using Open-Pour Liquid					
Dermal: SLNoGlove 2.9 HC SLWithGlove 0.023 HC Inhal. 0.0012 HC	0.1 lb ai/A	350 A/day	Dermal: SLNoGlove 1.45 SLWithGlove 0.012 Inhal. 0.0006	 32 3,900 3,700	 32 1,900
Aerial Applicator (Pilots not required to wear gloves)					
Dermal: SLNoGlove 0.0050 MC SLWithGlove Inhal 0.000068 MC	0.1 lb ai/A	350 A/day	Dermal: SLNoGlove 0.0025 Inhal. 0.000034	 19,000 65,000	 15,000
Applicator Open-cab Ground-boom					
Dermal: SLNoGlove 0.014 HC SLWithGlove0.014 MC Inhal. 0.00074 HC	0.1 lb ai/A	200 A/day	Dermal: SLNoGlove 0.004 SLWithGlove 0.004 Inhal. 0.00021	 12,00 12,000 11,000	 5,600 5,600

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Inhal. = Inhalation. Units = mg ai/pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate = Taken from the proposed label.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised July 5, 2000.
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated ÷ 70 kg body weight. Dermal unit exposures not corrected for dermal absorption since the dermal toxicological endpoints were derived from a 21-day dermal study. Inhalation assumes 100% absorption.
5. MOE = NOAEL ÷ ADD. Dermal NOAEL = 47 mg/kg bw/day. Inhalation NOAEL = 2.21 mg/kg bw/day.
6. MOEs may be combined when the dermal and inhalation toxicological effect is the same though identified from different studies. The convention used to combine is $1/(1/MOE_{DERMAL} + 1/MOE_{INHALATION})$.

An MOE of 100 is adequate to protect occupational pesticide handlers from exposures to bifenthrin. In this case, **provided mixer/loaders wear protective gloves,** all MOEs are >100. The lowest combined MOE is >1,800. Therefore these exposures are not of concern to HED.

8.2 Short-/Intermediate-Term Post-application Risk

Typically there is the possibility for agricultural workers to experience post-application exposure to dislodgeable pesticide residues. In conjunction with the Agricultural Re-Entry Task Force (ARTF), HED has identified a number of agricultural work activities that may result in post-application, re-entry exposure to pesticides. In addition, HED has identified surrogate transfer coefficients (TCs) in units of cm²/hr derived from exposure studies relative to "standard" agricultural work activities but which were conducted to assess exposure to other compounds.

For the proposed new crop uses, the activity with the highest TC is hand harvesting. For leaf petiole vegetables, hand harvesting has a TC of 2,500 cm^2/hr; hand harvesting for low-bush blueberries, the TC is 1,500 cm^2/hr; hand harvesting for high-bush blueberries, the TC is 5,000 cm^2/hr.

Since there are no chemical-specific data with which to assess post-application exposures to

agricultural workers, RD uses 5,000 cm^2/hr TC in conjunction with the assumption that 20% of the rate of application is available as dislodgeable foliar residue on day zero after application. The estimated post-application exposure is believed to be conservative (*i.e.,* protective).

The TCs used in this assessment are from an interim TC policy developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1 Revised 7 AUG 2000). It is the intention of HED's ExpoSAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. The following convention may be used to estimate post-application exposure to agricultural workers.

Surrogate Dislodgeable Foliar Residue:

DFR = application rate * 20 % available as dislodgeable foliar residue * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 or 1.08 x 10^{-3} ft^2/cm^2

and the Average Daily Dose

ADD = DFR (µg/cm^2) * TC (cm^2/hr) * hr/day * 0.001 mg/µg * 1/70 kg bw

$\therefore$ 0.1 lb ai/A * 0.20 * 4.54^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.225 µg/cm^2 and

0.225 µg/cm^2 * 5,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.128 mg/kg bw/day

Since MOE = NOAEL ÷ ADD then 47 mg/kg bw/day ÷ 0.128 mg/kg bw/day = 370

The MOE for the most highly-exposed post-application agricultural activity is greater than 100 (370). Therefore, the proposed uses are not of concern to HED. All other relevant post-application activities for the proposed use pattern are expected to have lower exposures therefore greater MOEs.

RESTRICTED ENTRY INTERVAL (REI)

The four product labels associated with this assessment list an REI of 12 hours. Bifenthrin is classified in Acute Toxicity Category III for acute dermal toxicity. It is classified in Acute Toxicity Category IV for acute inhalation toxicity, for primary eye irritation and primary skin irritation. It is not a dermal sensitizer. Therefore, the interim WPS REI of 12 hours is adequate to protect agricultural workers from post-application exposures to bifenthrin.

9.0 Data Needs and Label Requirements

9.1 Toxicology

- None.

9.2 Residue Chemistry

- Revised Section B/proposed label.
- Revised Section F/proposed tolerances.

9.3 Occupational and Residential Exposure

None.

Appendix 1: Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	00141199 (1984) Acceptable/guideline M: 0, 0.88, 3.8, 7.5, 15 mg/kg/day F: 0, 1.04, 4.3, 8.5, 17.2 mg/kg/day	NOAEL=M/F: 3.8/4.3 mg/kg/day LOAEL=M/F: 7.5/8.5 mg/kg/day based on increased incidence of tremors.
870.3150	90-Day oral toxicity (dog)	00141200 (1984) Acceptable/guideline 0, 2.21, 4.42, 8.84, 17.7 mg/kg/day	NOAEL =M/F: 2.21 mg/kg/day LOAEL = M/F: 4.42 mg/kg/day based on based on increased incidence of tremors.
870.3200	21/28-Day dermal toxicity (rat)	45280501 (2000) Acceptable/guideline 0, 23, 47, 93, 932 mg/kg/day	NOAEL = 47 LOAEL = 93 mg/kg/day based on staggered gait and exaggerated hindlimb flexion.
870.3200	21/28-Day dermal toxicity (rabbit)	00141198 (1984) Acceptable/guideline 0, 22, 44, 88 442 mg/kg/day	NOAEL = 88 mg/kg/day LOAEL = 442 mg/kg/day based on loss of muscle coordination and increased incidence of tremors.
870.3700a	Prenatal developmental in (rat, gavage)	00154482 (1983) Acceptable/non-guideline 0, 0.44, 0.88, 1.77, 2.2 mg/kg/day	**Maternal** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on tremors during gestation. **Developmental** NOAEL and LOAEL were not established (fetuses were not examined).
870.3700a	Prenatal developmental in (rat, gavage)	00141201 (1984) Acceptable/guideline 0, 0.44, 0.88, 1.77 mg/kg/day	**Maternal** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on tremors. **Developmental** NOAEL = 0.88 mg/kg/day LOAEL = 1.77 mg/kg/day based on increased fetal and litter incidence of hydroureter without nephrosis.
870.3700a	Prenatal developmental in (rat, diet)	45352301 (2001) Acceptable/guideline 0, 2.4, 4.8, 7.1, 15.5 mg/kg/day	**Maternal** NOAEL = 7.1 mg/kg/day LOAEL = 15.5 mg/kg/day based on clinical signs and decreased food consumption, body weight gains, and body weight gains (adjusted for gravid uterine weight). **Developmental** NOAEL = 15.5 mg/kg/day LOAEL was not established.
870.3700b	Prenatal developmental in (rabbit, gavage)	00145997 (1984) Acceptable/guideline 0, 2.36, 3.5, 7 mg/kg/day	**Maternal** NOAEL = 2.36 mg/kg/day, LOAEL = 3.5 mg/kg/day based on treatment-related head and forelimb twitching. **Developmental** NOAEL =7 mg/kg/day, LOAEL was not established.

Appendix 1: Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	00157225 (1986) Acceptable/guideline 0, 1.5, 3.0, 5.0 mg/kg/day	**Parental/Systemic** NOAEL = M/F: 5.0/3.0 mg/kg/day, LOAEL was not established in males. In females, LOAEL= 5.0 mg/kg/day based on tremors and decreased body weights. **Reproductive/ Offspring** NOAEL = 5.0 mg/kg/day, **Reproductive/ Offspring** LOAEL was not established.
870.4100b	Chronic toxicity (dog)	00163065 (1985) Acceptable/guideline 0, 0.66, 1.3, 2.7, 4.4 mg/kg/day	NOAEL = 1.3 mg/kg/day, LOAEL= 2.7 mg/kg/day based on increased incidence of tremors.
870.4300	Chronic/ Carcinogenicity (rat)	00157226 (1986) Acceptable/guideline M: 0, 0.6, 2.3, 4.7, 9.7 mg/kg/day F: 0, 0.7, 3.0, 6.1, 12.7 mg/kg/day	NOAEL = M/F: 4.7/3.0 mg/kg/day, LOAEL =M/F: 9.7/6.1 mg/kg/day based on increased incidence of tremors. **No conclusive evidence of carcinogenicity**
870.4300	Chronic/ Carcinogenicity (mouse)	00157227 (1986) Acceptable/guideline M: 0, 6.7, 25.6, 65.4, 81.3 mg/kg/day F: 0, 8.8, 32.7, 82.2, 97.2 mg/kg/day	NOAEL =M/F: 6.7/8.8 mg/kg/day, LOAEL = M/F: 25.6/32.7 mg/kg/day based on based on increased incidence of tremors. **Carcinogenic** potential was evidenced by a dose-related increase in the incidence of leiomyosarcomas in the urinary bladder, a significant dose-related trend for combined hepatocellular adenomas and carcinomas in males, and a significantly higher incidence of combined lung adenomas and carcinomas in females.
870.6200a	Acute neurotoxicity (rat, gavage)	44862102(1998) Acceptable/Guideline 0, 9.4, 32.8, 70.3 mg/kg/day	NOAEL = 32.8 mg/kg/day, LOAEL=70.3 mg/kg/day based on clinical signs of toxicity, FOB findings, altered motor activity, and mortality (females only).
870.6200b	Subchronic neurotoxicity screening battery (rat)	44862103 (1998) Acceptable/Guideline M: 0, 2.7, 5.6, 11.1 mg/kg/day F: 0, 3.5, 6.7, 13.7 mg/kg/day	NOAEL= M/F: 2.7/3.5 mg/kg/day, LOAEL= M/F: 5.6/6.7 mg/kg/day based on neuromuscular findings (tremors, changes in grip strength and landing foot-splay).

Appendix 1: Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6300	Developmental Neurotoxicity (rat)	46750501 (2006) Acceptable/non-guideline 0, 3.6, 7.2 and 9.0 mg/kg/day (gestation) 0, 8.3, 16.2 and 20.7 mg/kg/day (lactation)	**Maternal** NOAEL = 3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation, LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts). **Developmental** NOAEL =3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation. **Developmental** LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (increased grooming counts).